REMARKS

Status of the Claims

This paper amends claim 51, 63, and 64, and adds new claims 65-76. After the amendments set forth herein are entered, claims 51-76 are pending and under examination.

Support for the amendment to claims 51, 63, and 64 is found generally throughout the Specification and specifically at p. 2, ll. 22-28. Support for new claims 65-76 are found generally throughout the Specification and specifically at p. 1, ll. 13-19. No new matter is added by these amendments.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 54-56 and 63-64 stand rejected for lack of enablement. The Examiner alleges that the monoclonal antibodies designated B152 and B207 are not publicly available, rendering the claims encompassing the use of those antibodies not enabled. Applicants provide evidence herewith to demonstrate that the B152 and B207 antibodies are, in fact, publicly available.

Applicants disclose in the Specification that the B152 and B207 antibodies are available through the ATCC at Accession Nos.: HB-12467 and PTA-1626, respectively. Specification at p. 8, ll. 11-24 and p. 10, ll. 7-23. Hybridomas expressing these antibodies have been deposited and accepted by the ATCC, an International Depository Authority under the provisions of the Budapest Treaty. These antibodies are specifically referenced in U.S. Patent 6,627,457 (issued to Applicants) and, pursuant to the issuance of that patent, all restrictions upon public access to the deposits have already been irrevocably removed for the hybridomas.

Attached as Exhibit A is correspondence between Applicants' attorney and the ATCC Patent Depository regarding the accession numbers in question. The ATCC has confirmed that these antibodies are publicly available for general distribution, but do not appear in the ATCC

online catalog. Accordingly, this correspondence confirms that the antibodies are publicly available. This rejection should be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claim 51 stands rejected as indefinite based on the Examiner's assertion that it is unclear how the claimed method would work without a step of separation or washing to remove unbound ITA or hCG, or unbound detection antibody. The Examiner suggests that a claimed washing step is required for clarity. Applicants respectfully note that a variety of assay formats are routinely used which do not perform a specific washing step. For example, lateral flow assays (i.e., dipstick or test strip assays) are antibody-based assays that are well known in the art. These tests do not utilize a specific washing step. Accordingly, the lack of a washing step does not render the claim 51 indefinite or unclear. This rejection is traversed should be withdrawn.

Claim 51 stands rejected as indefinite on several additional grounds. Applicants respectfully submit that these rejections are traversed by the current claim amendments and should be withdrawn.

Claim 63 stands rejected as indefinite. This rejection is traversed by the current claim amendments and should be withdrawn.

Claim 53 stands rejected as indefinite for allegedly contradicting claim 51. Specifically, the Examiner alleges that a hydatidiform mole is a known pathologic condition of pregnancy, but claim 51, from which claim 53 depends, requires confirming that the subject is not pregnant. In support of this allegation, the Examiner refers to a definition of "hydatidiform mole" provided in conjunction with the Office Action mailed August 23, 2005. Applicants respectfully traverse this rejection.

A hydatidiform mole is considered an abnormal condition associated with a pregnancy. However, as noted in the description provided by the Examiner at paragraph 4, this condition is defined by a mole in which the embryo (i.e., fertilized egg) is either dead or absent. "The mole

itself is a collection of cysts that contain a jellylike substance and resemble a cluster of grapes." As noted in paragraph 5, the "chorionic villi around an aborting embryo degenerate and form clusters of fluid-filled sacs" (emphasis added). From this definition, it is clear that a hydatidiform mole is an interuterine lesion that is caused by a temporary but aborted pregnancy. The mole is *prima facie* evidence that the individual is not pregnant (i.e., carrying a viable embryo). Thus, contrary to the Examiner's allegation, a hydatidiform mole is not associated with a pregnant individual and, therefore, claim 53 is not in conflict with claim 51. Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 51-59 and 63-64

Claims 51-59 and 63-64 stand rejected as obvious over Cole et al. (Clin. Chem. 47: 308-315, 2001; "Cole") in view of O'Connor et al. (U.S. Patent 6,500,627; "O'Conner"), Birken et al. (Arch. Med. Res., 32: 635-643, 2001; "Birken"), Hochstrasser et al. (U.S. 2003/0157580; "Hochstrasser"), Chin et al. (U.S. 2002/0142305; "Chin"), and Bellet et al. (U.S. 2002/0192646). Applicants respectfully traverse this rejection.

The rejected claims encompass methods based on detecting both ITA (the hyperglycosylated form of hCG) and hCG for detection of trophoblastic disease. The lciamed method requires the use of two capture antibodies that bind to different epitopes of ITA and hCG, and a detection antibody. The total amount of detected ITA and hCG is used to diagnose the trophoblastic disease. In one embodiment, a single detection antibody is use which is capable of recognizing both ITA and hCG, resulting in a single detectable output representing the total combined amount of the proteins.

Cole discloses assays for individually measuring a variety of ordinary and irregular forms of hCG including nicked hCG, hCG lacking the β-subunit, the free β-subunit, asialo hCG, and hyperglycosylated hCG (ITA) for diagnosing trophoblastic disease. The Examiner acknowledges

that Cole fails to teach the use of antibodies to ITA (Office Action at p. 7, ¶ 3). Additionally, as related to the invention of claims 51-64, Cole does not disclose determining the total amount of two different hCG isoforms (e.g., ITA and hCG) for the purpose of diagnosing a trophoblastic disease.

O'Connor does not remedy this deficiency. O'Connor discloses a method for detecting gestational trophoblast disease (e.g., choriocarcinoma or hydatidiform mole) using two different capture antibodies for identifying different hCG isoforms, but does so for the purpose of obtaining a diagnostic ratio. At col. 9, ll. 35-67, O'Connor provides an assay using the B152 antibody to detect ITA ("the early pregnancy associated molecular isoform of hCG") and "a second capturing antibody which specifically binds to intact non-nicked hCG..." wherein the second antibody is B108 or B109. O'Connor then instructs to calculate the ratio of the signals associated with ITA and non-nicked hCG as an indicator of gestational trophoblast disease. O'Connor at col. 9, ll. 52-54. In contrast to the method of O'Connor, Applicants' method of claims 51-64 require that the a trophoblastic disease is identified based on the total amount (i.e.,, the sum) of the detected ITA and hCG.

Thus, the basic combination of Cole and O'Connor fails to provide an antibody-based assay for detecting trophoblastic disease based on detecting the total amount of ITA and hCG as the diagnostic indicator. O'Connor's method is based on determining a diagnostic ratio of ITA to non-nicked hCG, which is fundamentally different than Applicants' claimed method.

The remaining prior art references cited by the Examiner are secondary and do not specifically address the use of two different ITA capture antibodies for the detecting trophoblastic disease. Birken is cited merely to demonstrate that the B152 antibody is ITA-specific. The Examiner relies on Bellet to teach that the levels of hCG and the free hCGa subunit are elevated in patients having a tumor of trophoblastic origin relative to non-pregnant, healthy individuals. Applicants do not disagree with the Examiner's characterization of either Birken or Bellet, as currently applied. However, neither address the basic deficiency of Cole and

O'Connor; a failure to teach a diagnostic assay based on determining the total amount of ITA and hCG.

Hochstrasser is unrelated to the detection of trophoblastic disease and is cited for the pedestrian proposition that it is necessary to exclude alternative diagnoses when using diagnostic markers known to be associated with multiple conditions. Likewise, Chin is also unrelated to trophoblastic disease detection and cited for the general concept of baselining an assay against a normal population. Applicants do not disagree with the Examiner's characterization of either Hochstrasser or Chin, as currently applied. However, both of these references are unrelated to the use of ITA as a diagnostic. Furthermore neither reference discloses an antibody-based assay that uses two capture antibodies directed to different ITA epitopes.

In sum, claims 51-59 and 63-64 are unobvious over the cited prior art which fails to teach or suggest a diagnostic assay for trophoblastic disease based on determining the total amount of ITA and hCG. Applicants respectfully submit that this rejection is traversed and should be withdrawn.

This obviousness rejection based on Cole and O'Connor, in view of Briken, Bellet, Hochstrasser, and Chin, is inapplicable to new claims 65-76. The newly added claims encompass methods based on detecting ITA using two capture antibodies that recognize two different ITA epitopes. The use of two capture antibodies for ITA increases the sensitivity of the assay relative to those detecting ITA using a single capture antibody.

As noted above, Cole discloses assays for measuring a variety of ordinary and irregular forms of hCG for diagnosing trophoblastic disease, but fails to teach the use of antibodies to ITA (Office Action at p. 7, ¶ 3). Additionally, as related to claims 65-76, Cole does not disclose the use of two capture antibodies that bind to different epitopes of a single target molecule.

O'Connor discloses a method for using two different capture antibodies; however, the O'Connor method measures two different hCG isoforms for the purpose of obtaining a

diagnostic ratio. O'Connor does not suggest using two capture antibodies to detect the same antigen (ITA), as required by Applicants' amended claims.

Thus, the basic combination of Cole and O'Connor fails to provide an antibody-based assay which requires the use of two capture antibodies directed to different epitopes of the same antigen (ITA). It is Applicants' surprising discovery that the use of two different ITA capture antibodies increases the sensitivity of an ITA assay for the purpose of detecting trophoblastic disease.

The remaining prior art references cited by the Examiner are secondary and do not specifically address the use of two different ITA capture antibodies for the detecting trophoblastic disease. Birken is cited merely to demonstrate that the B152 antibody is ITA-specific. The Examiner relies on Bellet to teach that the levels of hCG and the free hCGa subunit are elevated in patients having a tumor of trophoblastic origin relative to non-pregnant, healthy individuals. Hochstrasser is unrelated to the detection of trophoblastic disease and is cited for the pedestrian proposition that it is necessary to exclude alternative diagnoses when using diagnostic markers known to be associated with multiple conditions. Chin is also unrelated to trophoblastic disease detection and cited for the general concept of baselining an assay against a normal population. None of these references address the basic difference between Applicants' method of claims 65-76 and the methods of Cole and O'Connor; a failure to teach an ITA detection assay using two capture antibodies directed to different ITA epitopes. Accordingly, this rejection is inapplicable to newly added claims 65-76.

Claims 60-62

Claims 60-62 stand rejected as allegedly obvious over Cole in view of O'Connor, Hochstrasser, Chin, Bellet, and Campbell et al. (U.S. Patent 4,946,958; "Campbell"). The Examiner applies Cole in view of O'Connor, Hochstrasser, Chin, and Bellet as discussed above, and further alleges that Campbell discloses a chemiluminescent label comprising an acridinium ester covalently linked to a monoclonal antibody. Applicants respectfully traverse this rejection.

Applicants submit that the detection method of claim 51, from which claims 60-62 depend, is unobvious over Cole in view of O'Connor, Hochstrasser, Chin, and Bellet, and the further addition of Campbell does nothing to address the deficiencies of this prior art combination. Although Campbell does disclose, generically, labeling monoclonal antibodies using acridinium esters, Campbell does not provide any teachings related to the use of ITA for detecting trophoblastic disease. In particular, Campbell does not suggest detecting ITA using two capture antibodies directed to different ITA epitopes. Accordingly, Applicants respectfully submit that this rejection is traversed and should be withdrawn.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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